TECHNICAL COMMENTARY

Musculoskeletal and connective tissue abnormalities

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Introduction

People with schizophrenia show increased rates of co-occurring conditions, including various disorders affecting the musculoskeletal system. Common disorders include; osteoporosis and the less severe osteopenia, which occur when bones lose minerals more quickly than the body can replace them, causing a loss of bone thickness; rheumatoid arthritis and systemic lupus erythematosus result from a malfunctioning immune system that mistakenly attacks healthy tissue; and ankylosing spondylitis is a type of inflammatory arthritis that mainly affects the spine.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- Moderate quality evidence finds small to medium-sized increased rates of fractures and osteoporosis in people with schizophrenia compared to controls. There may also be reduced rates of rheumatoid arthritis and ankylosing spondylitis. No significant differences were found in rates of osteopenia or systemic lupus erythematosus.

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Cullen AE, Holmes S, Pollak TA, Blackman G, Joyce DW, Kempton MJ, Murray RM, McGuire P, Mondelli V

Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis

Biological Psychiatry 2019; 85: 35-48

View review abstract online

Comparison	**Rates of non-neurological autoimmune disorders in people with schizophrenia or other psychotic disorders vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, mostly inconsistent, imprecise, direct) suggests small decreases in rates of rheumatoid arthritis and ankylosing spondylitis in people with schizophrenia or other psychotic disorders, with no differences in rates of systemic lupus erythematosus.**
Rheumatoid arthritis	
A small, significant effect of decreased rates of rheumatoid arthritis in people with psychosis; 12 population-level studies, OR = 0.65, 95%CI 0.50 to 0.84, $p < 0.001$, $I^2 = 80\%$, $p < 0.001$	
Ankylosing spondylitis	
A small, significant effect of decreased rates of ankylosing spondylitis in people with psychosis; 6 population-level studies, OR = 0.72, 95%CI 0.54 to 0.98, $p = 0.04$, $I^2 = 38\%$, $p = 0.14$	
Systemic lupus erythematosus	
No significant differences between groups; 7 population-level studies, OR = 0.95, 95%CI 0.65 to 1.39, $p = 0.80$, $I^2 = 77\%$, $p < 0.001$	
Consistency in results‡	Inconsistent, apart from ankylosing spondylitis
Precision in results§	Imprecise
Directness of results‖	Direct

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Leucht S, Burkard T, Henderson J, Maj M, Sartorius N

Physical illness and schizophrenia: a review of the literature

Acta Psychiatrica Scandinavica 2007; 116: 317-333

View review abstract online

Comparison	**Prevalence of osteoporosis and rheumatoid arthritis in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, unable to assess consistency or precision, direct) suggests increased rates of osteoporosis in people with schizophrenia, and reduced rates of rheumatoid arthritis.**
Osteoporosis and rheumatoid arthritis	
13 studies found increased rates of osteoporosis (reduced bone mineral density) in people with schizophrenia compared to controls. 16 studies found reduced rates of rheumatoid arthritis in people with schizophrenia compared to controls.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Stubbs B, De Hert M, Sepehry AA, Correll CU, Mitchell AJ, Soundy A, Detraux J, Vancampfort D.

A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia

Acta Psychiatrica Scandinavica 2014; 130: 470-486

View review abstract online

Comparison	**Prevalence of low bone mass in people with schizophrenia vs. controls.**

Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a medium-sized increased rate of osteoporosis, but not osteopenia, in people with schizophrenia compared to controls.**
Low bone mass	
Compared with controls, people with schizophrenia had a significant, medium-sized increased risk of osteoporosis, but not osteopenia; Osteoporosis: N = 1,824, OR = 2.86, 95%CI 1.27 to 6.42, p = 0.01 Osteopenia: N = 1,862, OR = 1.33, 95%CI 0.93 to 1.90, p = 0.10 *The prevalence of low bone mass in people with schizophrenia is around 50%;* Osteoporosis or osteopenia: 18 studies, N = 2,905, prevalence = 51.7% 95%CI 43.1% to 60.3%, I^2 = 93.8%, p < 0.001 Meta-regression revealed older age and male sex increased the prevalence of osteoporosis. Hyperprolactinemia, prolactin-raising antipsychotics, smoking status, duration of illness, and body mass index were not related to the prevalence of osteoporosis. Subgroup analyses revealed low bone mass was less prevalent in North America than in Europe, Asia, and less prevalent in mixed in-/out-patients than in-patients. Authors report no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Stubbs B, Gaughran F, Mitchell AJ, De Hert M, Farmer R, Soundy A, Rosenbaum S, Vancampfort D

Schizophrenia and the risk of fractures: a systematic review and comparative meta-analysis

General Hospital Psychiatry 37; 2015: 126-133

View review abstract online

Comparison	**Prevalence of fractures in people with schizophrenia vs. controls.**

Summary of evidence	**Moderate quality evidence (large sample, some inconsistency, unable to assess precision, direct) suggests increased rates of fractures in people with schizophrenia compared with controls.**
Fractures	
People with schizophrenia experience an increased rate of fractures compared to controls 5 studies, N = 168,914, IRR = 1.72, 95%CI 1.24 to 2.39, I^2 = 49% Authors report that antipsychotic medication was an important risk factor for fractures, and there was no evidence of publication bias.	
Consistency in results	Some inconsistency
Precision in results	Unable to assess
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IRR = incidence rate ratio, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[7].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[7].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[7];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[9].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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